REMARKS

Reconsideration of the rejections set forth in the Office action mailed October 25, 2002 is respectfully requested, in view of the discussion below.

I. Amendments

Claim 1 has been amended to specify that the antisense oligomer contains morpholino subunits, that the uncharged linkages are selected from phosphoramidate and phosphorodiamidate, and that the charged linkages are selected from charged phosphoramidate and phosphorodiamidate. See, for example, the description of preferred charged linkages in morpholino oligomers at page 15, lines 28-29, with reference to Figure 2B.

In addition, these claims have been amended to recite that the oligomer is effective to inhibit expression of the target sequence. See, for example, the specification at page 10, lines 6-7 or page 28, lines 21-22.

Claims 4 and 5 are amended to describe the structure of the phosphorodiamidate linkages without reference to a Figure. Support is found in Figure 2B, from which the linkage shown in the claim is derived.

In view of the above amendments and/or to expedite prosecution, claims 3, 14, 17, 19-23, 30-31, and 34-41 are cancelled. Dependencies are corrected where necessary.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

Claims 17, 19-23, 30-31 and 34-41 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation.

In view of the cancellation of these claims, this rejection is moot.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1, 3-6, 13-14, 17, 19-23, 30-31, and 34-41 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the Examiner's objections, the phrase "effective to hybridize to a target sequence, containing a translational start codon, within a bacterial nucleic acid which encodes an *E. coli secA* protein" in claim 1 has been amended to "effective to hybridize to a target sequence containing a translational start codon within a bacterial nucleic acid which encodes an *E. coli secA* protein, and thereby to inhibit expression of said target sequence". It should now be clearer that the target sequence, not the oligomer, contains a translational start codon. The applicant believes that this amendment addresses the first four specific objections under this section.

In response to the fifth specific objection, claims 4 and 5 have been amended to describe the structure of the phosphorodiamidate linkages without reference to a Figure, as noted above.

Claims 17, 19-23, 30-31, and 34-41 have been cancelled to expedite prosecution, as noted above.

In view of the foregoing, the applicants submit that the amended claims comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §103

Claims 1, 3-6, 13 and 14 were rejected under 35 U.S.C. §103 as being unpatentable over Zyskind *et al.* (U.S. Patent No. 6, 228,579) in view of Cook (U.S. Patent No. 6,239,265) and Arnold, Jr. *et al.* (U.S. Patent No. 6,060,456). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in independent claim 1, is directed to an antibacterial compound consisting of a substantially uncharged antisense oligomer containing from 10 to 40 morpholino subunits, each of said subunits supporting a base-pairing moiety effective to bind by Watson-Crick base pairing to a respective nucleotide base, said base-pairing moieties including a targeting nucleic acid sequence at least 10 nucleotides in length which is effective to hybridize to a target sequence containing a translational start codon within a bacterial nucleic acid which encodes an *E. coli secA* protein, and thereby to inhibit expression of said target sequence;

wherein adjacent subunits are joined by uncharged linkages selected from the group consisting of: uncharged phosphoramidate and phosphorodiamidate, or by charged linkages selected from the group consisting of charged phosphoramidate and phosphorodiamidate, and the ratio of

uncharged linkages to charged linkages in the oligomer is at least 4:1.

Results discussed at page 28, line 21 to page 29, line 6 of the present specification show that morpholino oligomers directed to various bacterial proteins inhibited growth of *E. coli* and *E. faecium* by up to 80%, at a concentration of 1.0 μM. The oligomers were effective when delivered in a conventional buffer vehicle (as described on page 34), suggesting that they are actively transported into the cells. As shown in Fig. 4B of the specification, an antisense morpholino oligomer of the claim, having the sequence presented as SEQ ID NO: 47, inhibited growth of *E. coli* by about 60% at a concentration of 0.1 μM, and by about 70% at a concentration of 1.0 μM.

B. The Cited Art

Zyskind *et al.* is directed to the use of exogenous nucleic acids which "produce antisense inhibitors of endogenous complementary mRNAs in a microorganism", for "identifying endogenous microbial proliferation genes" of the microorganism (Abstract). Accordingly, the "exogenous nucleic acid" is typically a DNA sequence effective to express an antisense inhibitor (see e.g. column 2, lines 25-27; column 5, lines 61-67; column 6, lines 59-61; and Examples 1-3). All three Examples employ plasmid DNA hundreds of basepairs in length.

The patent specification also devotes approximately one column to a discussion of antisense oligonucleotides. The reference teaches that such antisense oligonucleotides, typically 10-50 nucleotides in length, may be "of the type found in nature" (column 8, lines 37, 60-63), or they may be analogs such as phosphorothioates, methylphosphonates, or peptide nucleic acids (column 8, line 63 to column 9, line 40). There is no mention of morpholino oligomers. Antisense polynucleotides "having substantial sequence complementarity to the *E. coli* lepB, viaA, ddlB, orf1, and secA mRNAs" may be prepared and tested for antiproliferative effects, according to column 9, lines 25-40 of the reference.

However, no further guidance or exemplification is given with respect to such oligonucleotides; e.g. as to regions of mRNA to be targeted or means of entry of the oligonucleotides into bacterial cells. As noted above, the working examples are directed to the use of plasmid DNA, typically 500-1000 bp in length, which is transfected and expressed in the

cells. In particular, the "antisense RNA complementary to secA mRNA" disclosed by the reference (column 18, lines 27-30) is 836 bp in length, as shown in Figs. 11-12.

Arnold, Jr. *et al.* describes chimeric antisense oligonucleotides which are RNaseH-activating (e.g. Abstract; Field of the Invention; Summary of the Invention, column 4, lines 53-54). The exemplified compounds generally have a central "RNaseH Activating Region" having charged linkages selected from phosphorothioate, phosphodiester, and phosphorodithioate (see Table, column 7 of reference; also Tables at columns 45-48, 53-60, etc.).

Cook is directed to the preparation of oligonucleotides having chiral phosphorus-containing linkages, such as phosphorothioate, methylphosphonate, phosphotriester, or phosphoramidate, in a stereoselective manner, to produce compounds of "relatively high enantiomeric purity". See, for example, column 9, lines 22-29. As shown at column 8 of the patent, the oligonucleotides are composed of ribose or deoxyribose subunits.

C. Analysis

There is no suggestion in any of the references to employ substantially uncharged morpholino oligomers, as presently claimed. Zyskind includes a brief and general discussion of modified-DNA antisense oligonucleotides, with specific mention of phosphorothioates, methyl phosphonates, and peptide nucleic acids, in a disclosure primarily concerned with the use of plasmid DNA. The reference provides no suggestion to employ a substantially uncharged morpholino oligomer targeting a start codon region of *E. coli* secA protein.

Arnold, Jr. *et al.* stresses the importance of RNaseH activating ability in the chimeric oligonucleotides described in that reference; see, for example, the Abstract and the Field of the Invention. As noted in the applicant's specification at page 13, lines 24-28, morpholino oligomers are considered RNaseH inactive; therefore, this reference, even if combined with Zyskind, teaches away from the use of the claimed oligomers for antibacterial antisense applications.

Cook describes only ribose- or deoxyribose-based oligonucleotides, and the teachings of this reference, regarding enantiomerically pure oligonucleotides, provide no motivation to prepare or use the presently claimed morpholino oligomers.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §103.

V. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

LeeAnn Gorthey

Date: 4-24-03

LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
FAX: (650) 838-4350